"METHOD AND DEVICE FOR THE NON-INVASIVE ANALYSIS OF METABOLIC PROCESSES"

The invention relates to a method and an arrangement for the non-invasive analysis of control and regulation processes in human and animal metabolism, in order to be able to draw conclusions about specific illnesses from the changes of individual metabolism parameters.
Said method can be used in preventive analyses for the early detection of cancer, inflammatory diseases, and the determination of the need for antioxidants, for the therapy control of individual clinical pictures and the routine examination of occupational groups with specific physical and psychological stress.

For several years, analyses of fluorescence spectra have been known as highly accurate and very specific methods in basic research in biology as to transport processes by means of biological membranes and analyses in biomedicine as diagnostic auxiliary means and are currently in a steadily progressive developmental phase. The basis of the measuring methods is the knowledge of the properties of artificial fluorophores and the knowledge of the excitation and emission wavelengths of autofluorophores. A plurality of parameters relevant to metabolism such as tryptophan, adenosine triphosphate (ATP), guanosine triphosphate (GTP), nicotinamide adenine dinucleotide phosphate (NADP), nicotinamide adenine dinucleotide reduced (NADH), kynurenine, flavin adenine dinucleotide (FAD) and thromboxane have a so-called autofluorescence.

The determination of said autofluorescence has the advantage that the metabolism does not have to be supplied with non-physiological substances. For example, in the patent DE 35 42 167 A1, the changes of the autofluorescence of ascorbic acid during the oxidation process is used for the determination of the eye lens opacity in a non-invasive method.

Further works use the high native fluorescence of NADH for the detection of melanoma, DE 695 18 915 T2.

In the patent DE 32 10 593 A1, in an invasive method by means of an endoscope, the autofluorescence of the NADH is used for the determination of the oxido-reduction condition of organs.

In the patent DE 19 53 51 14 A1, the varying autofluorescence of biological tissue in the emission range from 520 to 600 nm is used for the diagnosis of cancerous tissue, with no specific biologically relevant substance being referred to. With this method, too, the measuring device has to be taken to the measuring site invasively by means of an endoscope.

After complex experiments, the fluorescence-spectrometric behaviour of biological tissues and organs was described with regard to a preventive cancer diagnosis in the patents US 59 83 125, US 57 69 081, US 53 69 496, US 60 91 985, US 60 80 584, US 63 46 101 B 1, US 2002 / 000 23 37 A 1, US 59 43 113, US 62 05 353 B1. For the analysis, the intensities of individual substances such as tryptophan, NADH and flavins, as well as the maximum fluorescence intensity in the wavelength range from 320 to 580 nm were considered. Additionally, the results of the Fourier analysis also considered.

In the analyses, the disadvantage could be determined that neither the use of the maximum fluorescence intensity in the wavelength range from 320 nm to 600 nm or the absolute fluorescence intensities of relevant metabolism parameters such as NADH, tryptophan, FAD and kynurenine nor the ratio of two substances such as NADH and kynurenine allows a clear separation between "healthy" and "cancerous".
Thus, e.g. a low ratio between the intensities of NADH and kynurenine is not only characteristic for cancer but all inflammatory diseases exhibit a similar ratio. This is not peculiar, since many cancerous diseases involve inflammations.
A further disadvantage of the invasive methods described above is the fact that by the stress load of the measuring process, a falsified momentary picture of the metabolism is given and no statements about metabolism regulatory processes are possible. Such a statement can only be made by measuring without stress, which can be repeated at short intervals or by measuring in a defined way as to time before and after a stress load.

The problem underlying the invention is the provision of a method and a device which allow a description of control and regulation processes in human and animal metabolism, in order to be able to draw conclusions about specific clinical pictures in the case of changes in these processes. The method is intended to make the actual measuring process non-invasive and quickly repeatable in order not to cause

a stress load by the measuring process.

According to the invention, the problem is solved by the features disclosed in the patent claims.

The advantages of the invention are the non-invasive measuring of fluorescence spectra and the lack of stress guaranteed thereby. Due to this measuring process, repeated measuring can take place at very short intervals and, thus, regulation processes in the metabolism can be recognised. By changes of these regulation processes under defined stress conditions, conclusions can be drawn about pathological changes of the organism.

In the following, the invention is illustrated in detail by means of an embodiment. The enclosed figures show:

Fig. 1 Block diagram of the recordation of the measurement readings

Fig. 2 Native fluorescence spectra

Fig. 3 Illustration of results of a simple biochemical model as selection stage

Fig. 4 Result of the separation of cancer diseases and inflammatory diseases

Fig. 5 Selection using the emission wavelengths 509 nm and 495 nm

By means of an optical measured section according to Fig. 1 consisting of a fibre optic cable 1 for the supply of the excitation light ray and an optic fibre cable 2 with collimator 3 for the diversion of the measuring signal, [1] is put at a suitable site of the body, preferably the crease between the thumb and the index finger. Both fibre optic cables 1; 2 are located in a carrier which is ergonomically formed, preferably a handpiece 4, and their outlets are preferably located vertically to each other.
A source of light 5 consisting of a laser or a controlled Xe flashlamp with a downstream monochromator or filter, produces the light for the excitation of the autofluorescence and is directed to the measuring site via the fibre optic cable 1. The wavelengths of the excitation light are preferably 287 nm, 305 nm, 326 nm and

[1] Translator's note: Sentence incomplete.

337 nm.
The fluorescent light emitted at the measuring site due to the excitation is collected by the collimator 3 and coupled into the fibre optic cable 2 and directed to a spectrometer 6. The spectrometer can have both a CCD line sensor and a photomultiplier with an upstream acusto-optical monochromator as transducer unit. The optical spectra which have been converted into electrical signals in the spectrometer 6, are now saved in a corresponding computing structure 7.

The fluorescence spectra saved in the computer consisting of the recorded wavelengths in the range of 287 nm to 600 nm and the corresponding fluorescence intensities, are prepared for analysis in a suitable table format.

Fig. 2 shows examples of said native spectra.

The value combinations (wavelength and fluorescence intensity) for metabolism-relevant, biologically active substances such as ATP, GTP, tryptophan, orotic acid, NADP, NADH, FAD etc. are selected from these tables. The excitation wavelengths and emission wavelengths of these substances were determined in complex pilot tests. Since different skin structures and skin components do not allow the use of the absolute values, further analysis can only take place with relative values. It is therefore necessary to determine value pairings of the relevant biologically active substances and to interrelate them in biophysical and biochemical models. These models contain substances which react with each other during the metabolism processes, are converted into each other and/or affect each other in their concentration and reactivity.

Fig. 3 shows the illustration of the result of a simple biochemical model which is used as the first selection stage of diagnosis, and which consists of the combination of NADH, kynurenine, FAD, NADP and thromboxane. This illustration demonstrates that even the use of five metabolism-relevant substances does not suffice to separate cancer diseases from inflammatory diseases. The first selection stage is only suitable to differentiate between "ill" and "healthy".
Subsequently, further selection stages take place in order to differentiate between inflammatory diseases and cancer diseases and also to detect a differentiation amongst the inflammatory diseases.

Fig. 4 shows a separation between cancer diseases and treated cancer diseases

and inflammatory diseases.
The analysis of the spectra by selection of the diseases by means of biophysical and biochemical models on the basis of biologically active substances known takes place at the same time as the analysis by means of self-learning systems which search for differences in the spectra of healthy probands and patients without using a known value pairing (wavelength and intensity) of biologically active substances.

Fig. 5 shows an additional selection at the wavelengths 509 nm and 495 nm, wherein the emitting substances have not been known so far, however, the use of this selection shows to be successful.

List of reference numbers

1. fibre optic cable for the supply of the excitation light
2. fibre optic cable for the diversion of the fluorescent light
3. collimator
4. handpiece
5. source of light
6. spectrometer
7. computing structure